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Clinical laboratory testing and in vitro medical devices — Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy

Laboratoires d'analyses de biologie médicale et dispositifs médicaux de diagnostic in vitro — Exigences relatives aux systèmes d'autosurveillance des traitements par anti-coagulant oraux

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems.*

This second edition cancels and replaces the first edition (ISO 17593:2007), which has been technically revised.

The main changes are as follows:

— Updated with more current state of the art information that has evolved over several years.

— Subclause 8.4 Validation of measurement precision: added a more robust study design.

— Subclause 8.5.8.2 and 8.5.8.3: updated examples were added to reflect changes in criteria.

— Subclause 8.6 Minimum acceptable system accuracy : Updated requirements/performance criteria.

— Clause 9 Lay person performance evaluation: added clarity, revised performance criteria and increased sample size.

— Removed Annex F listing of publications.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Oral-anticoagulation monitoring systems are in vitro diagnostic (IVD) medical devices that measure prothrombin time in fresh, untreated human blood specimens. Prothrombin time is an indicator of the ability of blood to clot. IVD medical devices for self-testing of oral-anticoagulation therapy are used predominantly by individuals who have heart valve replacements, or who are suffering from atrial fibrillation or deep vein thrombosis and are receiving oral anticoagulant therapy with vitamin K antagonist medicines (e.g. warfarin). Patients must maintain the level of anticoagulant in the blood high enough to reduce thrombin formation, yet low enough to avoid excessive bleeding. An oral-anticoagulation monitoring system allows the user to monitor anticoagulation therapy and take action to control the level of anticoagulant present in the blood. This document applies to oral-anticoagulation monitoring systems to be used by lay persons. The primary objectives are to establish requirements for oral-anticoagulation monitoring systems that will enable lay persons to achieve acceptable performance, and to specify procedures for manufacturers and other interested parties to demonstrate conformance of such systems to the requirements stated in this document.

Performance criteria for oral-anticoagulation monitoring systems were established, based on the state-of-the-art, which has been shown to offer significant benefit to patients [31]. The criteria are given in terms of "system accuracy", because metrological terms commonly used in International Standards (e.g. trueness and measurement uncertainty) would not be familiar to lay persons. System accuracy, which is affected by systematic bias and random effects (and is inversely related to measurement uncertainty), describes the degree to which the individual results produced by an oral-anticoagulation monitoring system agree with correct international normalized ratio (INR) values when the system is used as intended by lay persons. In setting the performance criteria, it is assumed that users will be properly selected and will receive the necessary training and that operating and control procedures will be followed in accordance with the manufacturer's instructions for use. It is also assumed that manufacturers will anticipate and mitigate the effects of reasonably foreseeable misuse, including reasonably foreseeable deviations from recommended operating and control procedures by the intended users.

Requirements that are unique to self-testing with oral anticoagulation monitoring systems, including specific content of information supplied by the manufacturer, are addressed in this document. General requirements that apply to all IVD medical devices and which are covered by other standards (e.g. IEC 61010-1, IEC 61010-2-101, ISO 13485, ISO 14971, ISO 23640 and ISO 18113-1, ISO 18113-4, ISO 18113-5) are incorporated by reference, when appropriate. While the goal is to standardize these requirements, it is also recognized that current national and regional usage by patients and regulatory authorities should be taken into consideration.

Clinical laboratory testing and in vitro medical devices — Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy

1 Scope

This document specifies requirements for in vitro measuring systems for self-monitoring of vitamin-K antagonist oral anticoagulation therapy, including performance, quality assurance and user training and procedures for the validation of performance by the intended users under actual and simulated conditions of use.

This document applies solely to prothrombin time measuring systems used by lay persons for monitoring their own vitamin-K antagonist oral anticoagulation therapy, and which report results as international normalized ratios (INR).

This document is applicable to manufacturers of such systems and those other organizations (e.g. regulatory authorities and conformity assessment bodies) having the responsibility for assessing the performance of these systems.

This document is not applicable to:

— in vitro measuring systems for coagulation quantities assessing vitamin-K antagonist oral anticoagulation therapy used by physicians or healthcare providers;

— non-vitamin-K antagonist oral anticoagulation therapy (e.g. dabigatran);

— a comprehensive evaluation of all possible factors that can affect the performance of these systems;

— the medical aspects of oral-anticoagulation therapy.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 15198, *Clinical laboratory medicine — In vitro diagnostic medical devices — Validation of user quality control procedures by the manufacturer*

ISO 17511, *In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples*

ISO 18113-1, *Clinical laboratory testing and in vitro diagnostic medical systems — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements*

ISO 18113-4, *Clinical laboratory testing and in vitro diagnostic medical systems — Information supplied by the manufacturer (labelling) — Part 4: In vitro diagnostic reagents for self-testing*

ISO 18113-5, *Clinical laboratory testing and in vitro diagnostic medical systems — Information supplied by the manufacturer (labelling) — Part 5: In vitro diagnostic instruments for self-testing*

ISO 20916, *In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice*

ISO 23640, *In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents*

IEC 60068-2-64:2008, *Environmental testing — Part 2: Test methods — Test Fh: Vibration, broad-band random (digital control) and guidance*

IEC 60601-1-2, *Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests*

IEC 61000-4-2, *Electromagnetic compatibility (EMC) — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test*

IEC 61000-4-3, *Electromagnetic compatibility (EMC) — Part 4-3: Testing and measurement techniques — Radiated, radiofrequency, electromagnetic field immunity test*

IEC 61010-1:2010, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 1: General requirements*

IEC 61010-2-101:2015, *Safety requirements for electrical equipment for measurement, control and laboratory use — Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment*

IEC 61326-1, *Electrical equipment for measurement, control and laboratory use — EMC requirements – Part 1: General requirements*

IEC 61326-2-6, *Electrical equipment for measurement, control and laboratory use — EMC requirements – Part 2-6: Particular requirements – In vitro diagnostic (IVD) medical equipment*

EN 13532, *General requirements for in vitro diagnostic medical devices for self-testing*

WHO Technical Report Series, No. 889, 1999, Annex 3 — *Guidelines for thromboplastins and plasma used to control oral-anticoagulant therapy*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 18113-1 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
accuracy
closeness of agreement between a measured quantity value and a true quantity value of a measurand

Note 1 to entry: For oral-anticoagulation monitoring systems, accuracy is measured by the extent to which measurements of *blood* (3.3) specimens from different patients agree with the *INR* (3.11) values traceable to a thromboplastin *international reference preparation (IRP)* (3.12).

[SOURCE: ISO/IEC Guide 99:2007, 2.13, modified — Notes 1, 2 and 3 to entry have been deleted, and a new Note 1 to entry has been added.]

3.2
bias
difference between the expectation of the test results and an accepted reference value

[SOURCE: ISO 5725-1:1994, 3.8, modified — Note 1 to entry has been deleted.]

3.3
blood
circulating intravascular tissue of the body, consisting of suspended formed elements and fluid plasma

Note 1 to entry: In this document, the term "blood" refers to fresh, untreated blood.

3.4
capillary blood specimen
blood (3.3) collected after puncturing minute vessels that connect the arterioles and venules

Note 1 to entry: Often obtained by pricking a fingertip, capillary blood is usually collected without additives.

3.5
control interval
statistically justified values specified as acceptable measured values obtained using a given quality control

3.6
control material
substance, material, or article intended by its manufacturer to be used to verify the performance characteristics of an in vitro diagnostic (IVD) medical device

Note 1 to entry: Control materials for anticoagulation monitoring can be reactive or nonreactive. A reactive control material participates in a reaction with the *reagent* (3.28) components. A nonreactive control does not react with the *reagent* (3.28) components, but may provide control functionality through other means, e.g. a simulation of the reaction [see *physical control* (3.24)].

3.7
healthcare provider
individual authorized to deliver healthcare to a patient

Note 1 to entry: In this document, a healthcare provider is an individual, e.g. a doctor, nurse, technician, technical specialist, or appropriate assistant, that provides instruction to a self-testing patient.

3.8
integrated control
quality control that is inherent in a *reagent* (3.28) component of a measuring system, intended by the manufacturer to verify the performance of the measuring system

Note 1 to entry: The integrated functional control is run concurrently with a patient measurement, includes a reactive component, and provides a functional check of the measurement procedure. The integrated control results shall be within a predefined measurement interval for the measured value to be displayed.

3.9
intermediate precision condition
condition of measurement, out of a set of conditions that includes the same *measurement procedure* (3.19), same location, and replicate measurements on the same or similar objects over an extended period of time, but may include other conditions involving changes

[SOURCE: ISO/IEC Guide 99:2007, 2.22, modified — Notes 1, 2 and 3 to entryhave been deleted.]

3.10
intermediate precision
measurement precision under a set of *intermediate precision conditions* (3.9) of measurement

Note 1 to entry: The concept of intermediate levels of precision is described in ISO 5725-3:1994[6].

Note 2 to entry: Quantitative measures of intermediate precision depend on the stipulated conditions.

Note 3 to entry: Intermediate precision provides an indication of the variability that will be experienced by a user during typical use.

[SOURCE: ISO/IEC Guide 99:2007, 2.23, modified — Note 1 to entry has been deleted and new Note 1 to entry, Note 2 to entry, and Note 3 to entry have been added.]

3.11
international normalized ratio
INR
patient's *prothrombin time* (3.26) measurement result, which has been standardized for the potency of the thromboplastin used in the *measurement procedure* (3.19) and expressed relative to a normal population average

Note 1 to entry: For a discussion of the use of INR, see Poller, et al[35].

3.12
international reference preparation
IRP
reference calibrator maintained by the World Health Organization

Note 1 to entry: The IRP for thromboplastin is directly calibrated for potency against the original British comparative thromboplastin preparations used in the establishment of the *international normalized ratio (INR)* (3.11) system.

3.13
international sensitivity index
ISI
factor that allows the conversion of a patient's *prothrombin time* (3.26) measurement result to *international normalized ratio* (3.11) values

Note 1 to entry: For a discussion of the use of ISI and *INR* (3.11), see Poller, et al[35].

3.14
lay person
user of an oral-anticoagulation monitoring system who does not have specific formal medical, scientific, or technical knowledge related to oral-anticoagulation monitoring

Note 1 to entry: "Lay person" also includes, for example, a person's family member who performs the testing.

3.15
liquid quality control
liquid material that mimics patient specimens and monitors the testing process from specimen application to result interpretation

3.16
manufacturer's selected measurement procedure
measurement procedure (3.19) that is calibrated by one or more primary or secondary calibrators when available.

[SOURCE: ISO 17511:2020, 3.43, modified — Notes 1, 2 and 3 to entry have been deleted.]

3.17
manufacturer's standing measurement procedure
measurement procedure (3.19) used to assess (or assign values to) the end-user's calibrator

Note 1 to entry: A standing measurement procedure may be calibrated with a reference method or with the manufacturer's "working" or "master" calibrator.

3.18
manufacturer's working calibrator
working measurement standard
standard that is used routinely at the manufacturer's laboratory to calibrate or check material measures, measuring instruments or reference materials

Note 1 to entry: This standard is used routinely at the manufacturer's laboratory to calibrate or check material measures, measuring instruments or reference materials.

Note 2 to entry: This applies to a thromboplastin preparation used by the manufacturer during the preparation of a *prothrombin time (PT)* (3.26) reagent mixture.

Note 3 to entry: The assigned value of the manufacturer's working calibrator is metrologically traceable to that of the *international reference preparation (IRP)* (3.12).

3.19
measurement procedure
detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measuring model and including any calculation to obtain a measurement result

[SOURCE: ISO/IEC Guide 99:2007, 2.6, modified — Notes 1, 2 and 3 to entry have been deleted.]

3.20
measurement reproducibility
reproducibilitymeasurement *precision* (3.25) under *reproducibility conditions* (3.31) of measurement

[SOURCE: ISO/IEC Guide 99:2007, 2.25, modified — Note 1 to entry has been deleted.]

3.21
measuring interval
set of values of quantities of the same kind that can be measured by a given measuring instrument or measuring system with specified instrumental measurement uncertainty, under defined conditions

Note 1 to entry: In some fields, the term is "measuring range" or "measurement range".

Note 2 to entry: This represents the interval of examination results over which the performance characteristics have been validated by the manufacturer.

[SOURCE: ISO/IEC Guide 99:2007, 4.7, modified — Note 2 to entry has been deleted and a new Note 2 to entry has been added.]

3.22
metrological traceability
property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties

3.23
oral anticoagulant
vitamin K antagonists (e.g. warfarin) and non-vitamin K antagonist (e.g. direct oral anticoagulant) agents used for treating and preventing thromboembolic events

3.24
physical control
control device that does not include chemically reactive components and that is intended by the manufacturer to verify the performance of the instrument

Note 1 to entry: The physical control system may be in the form of an electronic device that provides a simulated reaction.

Note 2 to entry: The physical control result shall be within predefined limits, in order for the measuring system to be considered properly functional.

3.25
precision
closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions

Note 1 to entry: Measurement precision is usually expressed numerically by measures of imprecision, such as standard deviation, variance, or coefficient of variation (CV) under the specified conditions of measurement.

Note 2 to entry: The 'specified conditions' can be, for example, *repeatability conditions* (3.29), *intermediate precision conditions* (3.9), or *reproducibility conditions* (3.31). See ISO 5725-1:1994.

Note 3 to entry: Measurement precision is used to define *repeatability* (3.30) of measurement, *intermediate precision* (3.10), and *measurement reproducibility* (3.20).

Note 4 to entry: Sometimes "measurement precision" is erroneously used to mean measurement accuracy.

[SOURCE: ISO/IEC Guide 99:2007, 2.15]

3.26
prothrombin time
PT
time required to clot a *blood* (3.3) specimen once exposed to a thromboplastin or tissue-factor derived *reagent* (3.28) material

3.27
prothrombin time measuring system
measuring system that records the time required for a specimen to clot after being exposed to a thromboplastin or tissue-factor derived *reagent* (3.28)

Note 1 to entry: The system includes the *reagent* (3.28) plus the instrument used to record the clotting time.

3.28
reagent
part of the in vitro diagnostic (IVD) medical device that produces a signal via a chemical or electrochemical reaction, which allows the quantity to be detected and its value measured in a specimen

3.29
repeatability condition
condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time

Note 1 to entry: Repeatability condition is essentially unchanging conditions, intended to represent conditions resulting in minimum variability of measurement results.

Note 2 to entry: For the purposes of this document, "laboratories" should be interpreted as "locations".

[SOURCE: ISO/IEC Guide 99:2007, 2.20, modified — Notes 1 and 2 to entry have been deleted, and new Notes 1 and 2 to entry have been added.]

3.30
repeatability
measurement *precision* (3.25) under a set of *repeatability conditions* (3.29) of measurement

[SOURCE: ISO/IEC Guide 99:2007, 2.21]

3.31
reproducibility condition
condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects

[SOURCE: ISO/IEC Guide 99:2007, 2.24, modified — Notes 1 and 2 to entry have been deleted.]

3.32
secondary reference measurement procedure
measurement procedure (3.19) that is calibrated by one or more primary calibrators

Note 1 to entry: The *measurement procedure* (3.19) for *prothrombin time* (3.26) measurements is sometimes referred to as a "secondary standard procedure".

3.33
system accuracy
closeness of agreement of a set of representative measurement results from a measuring system and their respective reference values

Note 1 to entry: The term *accuracy* (3.1) of measurement, when applied to a set of measurement results, involves a combination of random error components and a common systematic error or *bias* (3.2) component.

Note 2 to entry: Reference values are assigned by a *measurement procedure* (3.19) traceable to a reference measurement procedure of higher order.

Note 3 to entry: System accuracy may be expressed as the interval that encompasses 95 % of the differences observed between the results of the system being evaluated and their reference values. This interval also includes measurement uncertainty from the *measurement procedure* (3.19) used to assign the reference values.

3.34
trueness
agreement between the average value obtained from a large series of measurement results and an accepted reference value

Note 1 to entry: A measure of trueness is usually expressed as *bias* (3.2).

3.35
type test
test of one or more samples of equipment (or parts of equipment) made to a particular design, to show that the design and construction meet one or more requirements of the applicable standard

Note 1 to entry: Statistical sampling is not required for a type test.

[SOURCE: IEC 61326-1:2012, 3.1.13, modified — Note 1 to entry added.]

3.36
user comformance
ability and willingness of the user of a measuring system to adhere to and operate within the defined specifications of a *measurement procedure* (3.19)

3.37
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The word "validated" is used to designate the corresponding status.

Note 2 to entry: The use conditions for validation can be real or simulated.

Note 3 to entry: In design and development, validation concerns the process of examining an item to determine conformity with user needs.

Note 4 to entry: Validation is normally performed during the final stage of development, under defined operating conditions, although it may also be performed in earlier stages.

Note 5 to entry: Multiple validations may be carried out if there are different intended uses.

[SOURCE: ISO 9000:2015, 3.8.13, modified — Note 1 to entry was deleted and Notes 3, 4 and 5 to entry have been added.]

3.38
venous blood specimen
blood (3.3) collected after directly puncturing a vein, usually with a needle and syringe, or another collection device

Note 1 to entry: Venous blood may be collected without additives such as anticoagulants or preservatives, and if so, will be inherently unstable. Venous blood may also be collected in containers containing additives or preservatives with the intent to stabilize specific components.

3.39
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The word "verified" is used to designate the corresponding status.

Note 2 to entry: Design verification is the application of tests and appraisals to assess conformity of a design to the specified requirement.

[SOURCE: ISO 9000:2015, 3.8.12, modified — Notes 1 and 2 to entry were deleted and new Note 2 to entry has been added.]

3.40
volume fraction of erythrocytes in blood
proportion of packed cells in a *blood* (3.3) specimen

Note 1 to entry: It is expressed as a fraction, but often given as a percentage (conventional) of the SI unit.

Note 2 to entry: It is sometimes referred to as "haematocrit", after the instrument originally used to estimate the volume fraction of erythrocytes in *blood* (3.3).

4 Design and development

4.1 General requirements

The requirements specified in ISO 13485 apply.

The requirements specified in EN 13532 apply to evaluation of the performance of the oral-anticoagulation monitoring system.

4.2 Measuring interval

The measuring interval of the system shall be at least 1,0 to 6,0 INR.

4.3 Safety

The requirements specified in IEC 61010-1 and IEC 61010-2-101 apply.

4.4 Risk management

4.4.1 Identification of hazards

The manufacturer shall decide upon the identification of potential hazards from knowledge of factors including, but not limited to, the following:

a) intended use of the product;

b) users' skills and limitations;

c) protection against unintentional change of settings (e.g. units reported);

d) likely deviations from recommended operating and control procedures;

e) influence of interfering substances.

NOTE Guidelines for evaluating potentially interfering substances are found in CLSI document EP07 [22].

4.4.2 Risk management

The requirements specified in ISO 14971 apply.

In performing risk assessment, the manufacturer shall consider:

a) severity of harm (e.g. potential harm to the patient),

b) probability of occurrence of harm (e.g. insufficient specimen volume or incorrect reagent unit placement), and

c) probability of the system failing to detect the mistake (e.g. deficient internal instrument sensors).

NOTE 1 This document does not specify levels of risk acceptability.

NOTE 2 Guidelines for identifying potential hazards from the use of "unit use devices" are found in CLSI document EP18-A2 [24].

NOTE 3 ISO TR 24971 provides guidance on the application of ISO 14971. Risk management includes risk analysis, risk evaluation, risk reduction and risk control.

4.5 Ergonomic and human factor aspects

The design of the oral-anticoagulation monitoring system shall take into consideration relevant ergonomic and human factors including, but not limited to, the following:

a) User aspects:

   1) selection;

   2) training;

   3) compliance.

b) User environment:

   1) temperature;

   2) humidity.

c) System properties:

   1) shock resistance;

   2) stability of reagents.

d) User interface:

   1) ease of operation;

   2) protection from typical "wear and tear" that can be encountered in the use environment;

   3) readability of reported results;

   4) fault conditions and error messages;

   5) unambiguous messages to the user (e.g. "low battery" or "low result") rather than only "low";

6) user verification of proper system function;

7) user verification of out-of-date reagents, calibrators, controls.

4.6 Quality assurance and risk controls

4.6.1 General

Quality assurance of oral anticoagulation monitoring systems consists of multiple elements. See Annex D for descriptions of the various elements of quality assurance that may apply.

The manufacturer shall provide system-specific risk control measures, as required by the risk management plan. The requirements specified in ISO 14971 apply.

The risk control measures, including any limitations, shall be described in the instructions for use and the training program as appropriate.

Risk control measures shall address the education and training of users and healthcare providers (see Clause 7), as well as the elements in 4.6.2 to 4.6.4.

4.6.2 Measurement verification

Each measurement reported by the oral-anticoagulation monitoring system shall be verified by the measuring system.

The nature and extent of internal verification to be performed by the measuring system shall be determined by the results of the risk analysis.

4.6.3 Control of system performance

The manufacturer shall provide a control procedure and instructions for the use of quality control(s).

The quality control procedure shall be validated. The requirements specified in ISO 15198 apply.

Quality control(s) may consist of a liquid control, an integrated control, a physical control, or a combination of controls.

The manufacturer shall provide instructions for when control(s) shall be used, and where appropriate, control interval, and actions to be taken when controls are out-of-range.

4.6.4 Verification of self-testing performance

The manufacturer shall recommend a procedure and acceptance criteria for users to verify the acceptability of self-testing results.

Verification may be based on a comparison between results obtained by the user and a healthcare provider at specified intervals. An interval of six months or less is recommended. With new self-testers, more frequent intervals can be necessary to verify the technique, e.g. monthly.

4.7 Metrological traceability

The requirements specified in ISO 17511 shall apply to the manufacturer's process for calibrating the oral-anticoagulation monitoring systems.

The measurement results of the manufacturer's selected and/or standing measurement procedure shall be traceable to those of the World Health Organization (WHO) manual tilt-tube measurement procedure using an International Reference Preparation (IRP) of thromboplastin as referenced in 8.5.5.

NOTE 1 The WHO tilt-tube measurement procedure uses fresh, citrated plasma, whereas systems for self-testing use fresh, untreated blood. Calibration of the systems involves parallel measurement of fresh plasma and blood from the same patients. In this case, the blood specimens are the calibrator.

If the manufacturer's standing measurement procedure uses blood, then calibration of the procedure against the WHO IRP and tilt-tube method shall occur through parallel measurement of blood and plasma. Calibration of the end-user's routine measurement procedure shall use blood.

If the manufacturer's standing measurement procedure uses plasma, then plasma shall be used to calibrate the procedure against the WHO IRP and tilt-tube method. Parallel measurement of plasma and blood shall occur during calibration of the end-user's routine measurement procedure (e.g. using the same lot of reagents).

The traceability chain should include as few steps as practical, to minimize combined standard measurement uncertainty.

NOTE 2 An example of a traceability chain for a typical factory-calibrated oral-anticoagulation monitoring system is shown in Figure B.1. The illustration of a full traceability chain is taken from ISO 17511:2020. This example is not intended to represent the only possibility of a suitable traceability chain.

Control measures shall be implemented within each step of the calibration process, in order to monitor, assess and control drift and variability.

NOTE 3 The process capability index (Cpk) can be used to define and detect unacceptable drift [32].

Calibration of the manufacturer's standing measurement procedure shall be verified at predefined intervals against the manufacturer's selected measurement procedures. ISO 15193 and ISO 15194 may be used as guides.

The manufacturer's working calibrator may be a representative panel of fresh capillary or venous blood specimens that span the measuring interval to ensure commutability of the calibrator between reference measurement procedures, or secondary reference measurement procedure. Manufacturers should define the procedure and the time period during which the fresh specimens may be used.

5 Information supplied by the manufacturer

5.1 General requirements

The information supplied to users by the manufacturer shall be clear and concise, using plain terms that are readily understood by a lay person.

The information shall be well organized and easy to read.

Symbols and illustrations should be used where appropriate. Symbols shall conform to International Standards, e.g. ISO 15223-1. If symbols are used for which no standard exists, the symbols shall be described within the text.

The language(s) of the country in which the oral-anticoagulation monitoring system is distributed may need to be considered. Additional languages are optional.

The content of instructions for use shall be understandable by lay persons. Instructions for use shall include a revision number, or the year and month of issue.

In addition to the requirements specified in ISO 18113-5, the oral-anticoagulation monitoring instrument shall also be identified by labels including the following information name or trade name of the manufacturer and address of the manufacturer;

a) Unique device identifier (UDI);

   1) Where the in vitro diagnostic (IVD) instrument is subject to unique identification rules, labels shall include the unique device identification including the UDI carrier (AIDC format), and Human Readable Interpretation (HRI)

      NOTE 1 The content, format, and size of the UDI is defined by the accredited UDI issuing agency selected.

   2) When AIDC carriers other than the UDI Carrier are part of the product labelling, the UDI carrier shall be readily identifiable.

      NOTE 2 HRI text is not the same as the text that is already placed on the label and is a legible interpretation of the data characters encoded in the UDI Carrier.

   3) The UDI shall include both the UDI-DI (device identifier) and the UDI-PI (production identifier) unless specifically exempted by regulations.

   4) For the IVD instrument, the UDI-PI shall include at least serial number unless the instrument is managed by batch code, in which case the batch code shall be included.

      NOTE 3 If there also is a manufacturing date on the label for reasons other than production control purposes, it does NOT need to be included in the UDI-PI unless required by specific regulation.

   5) If there are significant constraints limiting the use of both AIDC and HRI on the label, the AIDC format shall be generally preferred except for environments where HRI is more appropriate to the user.

   6) The UDI Carrier should be readable during normal use, storage conditions, and throughout intended life of the IVD reagent. Refer to ISO/IEC 15415 for quality control criteria.

   7) The placement of the UDI Carrier should be done in a way that AIDC method can be accessed during normal operation or storage.

   8) The UDI may be placed on a separate label from other required information.

   9) A single finished IVD instrument made up of multiple parts that have to be assembled may have the UDI Carrier only on one part.

   10) Local, national, or regional regulations can apply.

b) a reference to the user manual or instructions for use.

c) information on the liquid quality controls intended to be used with the device.

d) Limitations to the procedures (e.g. interferences, effect of under-sampling or over-sampling on the INR result).

e) Sample volume required for the test (e.g. 8 µL).

f) Materials included and materials not included in the test kit.

5.2 Instructions for use of the oral-anticoagulation monitoring system

The system shall be accompanied by instructions for use, from the requirements set out in ISO 18113-5. The following information shall also be included:

a) where applicable, trade name or registered trademark and address of the manufacturer, the name and address of the distributor, if applicable, and how to access help;

b) manufacturer's standing measurement procedure (comparator method) and/or reference material designated by the manufacturer to evaluate performance characteristics;

c) type of specimens used by the manufacturer for calibration (e.g. blood or plasma);

d) measurement procedure to be followed when using the system, including:

   1) the sequence of steps to prepare the instrument for the measurement, to perform the measurement (including the volume and recommended appearance of the specimen) and to maintain the instrument;

   2) the sequence of adjustment (e.g. use of a number, code strip, code chip), measurement and verification, and the allowed time intervals between them;

   3) the measurement units reported by the system for the INR values;

   4) advice on how to proceed when error messages, unexpected results or results outside the specified measuring interval are generated by the instrument.

e) environmental conditions (e.g. temperature and relative humidity) in which the system may be used;

f) description of instrument cleaning procedures;

g) when instruments are reprocessed for a new user, disinfection procedures and description of a reset function or procedure to ensure the results from the previous user are deleted, if applicable;

h) precautions to be taken to prevent system damage, e.g. from electrostatic discharge, magnetic fields, and heat, humidity, shock and other external influences or other environmental conditions, as applicable (see IEC 61010-2-101:2015, Clause 5);

i) description and explanation of any symbols used on labels and in the instructions for use;

j) guidance on action to be taken by the user as a consequence of the result, including:

   1) a reference to the instructions given by a healthcare provider, and a warning not to deviate from these instructions on the basis of the result without consulting the healthcare provider;

   2) advice on how to proceed if the result is questionable to the user;

   3) indication of how the monitoring system alerts the user when the result is outside the specified measuring interval (e.g. error messages, fault notifications).

The instructions for use shall state what actions to take if the verification indicates an invalid result.

5.3 Labels for the reagents and control(s)

The reagents and control(s) shall be identified by a label or labels.

The requirements specified in ISO 18113-4 apply.

In addition, the following information shall be included on the label(s):

— a reference to the instructions for use;

— UDI;

— the instrument specified to be used with the reagents.

Warning statements should be included on the label concerning:

— use of the reagents with the specified oral-anticoagulation monitoring instrument to promote reliable measurement results;

— safe disposal of the reagents after use.

The language(s) of the country in which the reagents and control materials are distributed shall be used; additional languages are optional.

5.4 Instructions for use of reagents and control materials

Reagents and control materials provided for use with an oral-anticoagulation monitoring system shall be accompanied by instructions for use.

The requirements specified in ISO 18113-4 apply.

In addition, the following information shall be included in the instructions for use:

a) an indication of how to access help from the manufacturer and/or distributor;

b) the instrument specified to be used with the reagents and control material;

c) the international sensitivity index (ISI) of the reagent;

d) the storage conditions (e.g. temperature, humidity, exposure to light);

e) a warning statement (for reagents) concerning the need to tightly seal the cap of the immediate container to protect reagent strips or sensors from exposure to air;

f) the measuring interval, indicating the upper and lower limits within which INR results are reported;

g) the measurement procedure used to evaluate the performance characteristics of the system, and a statement describing the metrological traceability of measurement results to a reference measurement procedure or reference material of higher order;

h) the measurement procedure to be followed including:

   1) the sequence of steps to prepare the reagents and execute the measurement;

   2) the timing between the individual steps, if applicable;

Required information regarding reagents and/or control materials may be included in the instructions for use of the instrument or system if the manufacturer of the instrument or system is the same as the manufacturer of the reagents. If there is a change in this information, the changed information shall be placed in the instructions for use for the reagents.

6 Safety and reliability testing

6.1 General requirements

6.1.1 Protocol

Safety and reliability testing shall be performed by the manufacturer according to a written protocol. The protocol shall, as a minimum, specify the test designs, including the number of instruments, reagent units and replicate measurements per instrument, and the data analysis procedures and acceptance criteria. The results of the safety and reliability testing shall be documented in a report.

Specified testing requirements are minimum requirements.

For performance tests, the protocol shall include a statistical rationale for the test design.

NOTE 1 The tests described in 6.2 to 6.8 are type tests.

NOTE 2 The tests described in 6.9 to 6.12 are performance tests.

6.1.2 Instruments and reagents

Instruments and reagents selected for testing shall be representative of routine production units.

For type tests, at least three instruments shall be used in each test.

For performance tests, at least ten instruments shall be used in each test.

6.1.3 Acceptance criteria

Acceptance criteria for bias and repeatability for the performance tests in 6.10 to 6.13 should be derived from the system accuracy criteria in 8.6.1. The rationale for the acceptance criteria shall be documented in the protocol.

The oral-anticoagulation monitoring system shall either pass the acceptance criteria in each test protocol or the system shall be rendered non-functional and shall not display a numerical INR result.

Failures to meet acceptance criteria shall be investigated.

6.2 Protection against electric shock

The requirements specified in IEC 61010-1:2010, Clause 6, apply.

6.3 Protection against mechanical hazards

The requirements specified in IEC 61010-1:2010, Clause 7, apply.

6.4 Electromagnetic compatibility

The requirements specified in IEC 61326-1, IEC 61326-2-6 and IEC 60601-1-2 apply. Minimun requirements are mentioned in Annex A.

In addition, if the monitoring system can be connected to other equipment, such as a computer or cell phone, then the electromagnetic compatibility (EMC) test shall also be performed; unless the monitoring system is incapable of performing a test when connected.

6.5 Resistance to heat

The requirements specified in IEC 61010-1:2010, Clause 10, apply.

6.6 Resistance to moisture and liquids

The requirements specified in IEC 61010-1:2010, 11.1, 11.2 and 11.3 apply.

6.7 Protection against liberated gases, explosion, and implosion

The requirements specified in IEC 61010-1:2010, 13.1 and 13.2.2 apply.

6.8 Instrument components

The requirements specified in IEC 61010-1:2010, 14.1, 14.4, 14.5 and 14.6 apply.

6.9 Performance test

The performance test shall be performed before and after each determination of mechanical resistance to shock, vibration and impact (see 6.10) and protection against exposure to temperature and humidity levels (see 6.11 and 6.12). Pass/fail criteria shall be based on the effect of the challenge on system bias and repeatability.

Prior to each performance test, the oral-anticoagulation monitoring instrument shall be equilibrated to 23 °C ± 2 °C. The manufacturer's recommended control material or a suitable alternative should be used for the performance tests.

It can be difficult to separate the variability due to specimen and reagent components from the variability due to instrument components. This should be taken into consideration when designing the test and developing acceptance criteria.

A check strip, which simulates a reagent strip after reaction, or other suitable control material, may be used to verify that system performance has not been affected.

Electronic control systems may report results in units (e.g. mV) different from those reported for blood specimens. In this case, the average and repeatability of the values reported by the system may be used.

The order of measurement of test samples shall be specified in the protocol.

The average INR value and repeatability variance along with 95 % two-sided confidence interval shall be calculated before and after each challenge, and the result compared to the acceptance criteria.

a) Bias: the difference between the average INR value after the challenge and the average INR value before the challenge along with 95 % two-sided confidence interval shall be calculated and compared to the acceptance criteria for bias.

b) Repeatability: the ratio of the repeatability standard deviation after the challenge to the repeatability standard deviation before the challenge along with the 95 % two-sided confidence interval for this ratio shall be calculated. The confidence interval for the ratio of two standard deviations is based on the ratio of variances which follows a F-distribution [43]. An Acceptance Criteria for the ratio may have been established, if not then the acceptability of the ratio will be based on the acceptability of the standard deviation. For example, if the Acceptance Criteria for repeatability coefficient of variation (%CV) is 5 % and the %CVs before and after the challenge are 1 % and 2 %, respectively, the doubling of the %CV may still be acceptable.

6.10 Mechanical resistance to shock, vibration, and impact

6.10.1 Vibration test protocol

Perform the performance test described in 6.9.

Perform the vibration test as specified in IEC 60068-2-64:2008, 8.3.

After vibration testing is complete, repeat the performance test.

The requirements specified in IEC 60068-2-64:2008, 8.3 apply.

6.10.2 Drop test protocol

To verify resistance to damage from dropping, perform the baseline performance test as specified in 6.9.

Perform the drop test as specified in IEC 61010-1:2010, 8.2.

After drop testing is complete, repeat the performance test.

The requirements specified in IEC 61010-1:2010, 8.2 apply.

6.11 Temperature exposure limits

6.11.1 High-temperature test protocol

Perform the performance test as specified in 6.9.

Place the instrument in an environmental chamber that can be monitored for internal temperature.

Increase the temperature to 50 °C ± 2 °C and leave the instrument at this temperature for 8 h in the chamber.

Remove the instrument from the environmental chamber and allow it to cool to a temperature of 23 °C ± 2 °C and repeat the performance test.

For those systems in which the reagents are an integral component of the instrument and cannot be separated from the system, the high-temperature exposure conditions shall be limited to the use conditions specified by the manufacturer.

6.11.2 Low-temperature protocol

Perform the performance test as specified in 6.9.

Place the instrument in an environmental chamber that can be monitored for internal temperature.

Decrease the temperature to –20 °C ± 2 °C and leave the instrument at this temperature for 8 h in the chamber.

Allow the instrument to reach a temperature of 23 °C ± 2 °C in the environmental chamber to avoid condensation from the moist outside air contacting the cold instrument. Remove the instrument from the chamber and repeat the performance test.

For those systems in which the reagents are an integral component of the instrument and cannot be separated from the system, the low-temperature exposure conditions shall be limited to the use conditions specified by the manufacturer.

6.12 Humidity-exposure test protocol

Perform the baseline performance test as specified in 6.9.

Place the instruments in a temperature- and humidity-controlled chamber.

Stabilize the relative humidity, noncondensing to 90 % ± 3 %, and the temperature to 32 °C ± 2 °C.

Leave the instruments in the chamber for 48 h at the specified temperature and humidity.

Transfer the instruments from the chamber to ambient conditions of relative humidity < 60 % and a temperature of 23 °C ± 2 °C, and wait 15 min.

Assessment of the degree and effects of moisture absorption is the purpose of this test. Any moisture absorbed by the system during the time in the chamber is intentionally retained. The temperature should approach ambient during the 15 min delay, but complete equilibration is not required.

Repeat the performance test.

6.13 Reagent and storage and use testing

Conditions for the storage, use and transport of reagents and control materials shall be defined and verified.

Stability of reagents and control materials through the expiration dates shall be demonstrated. The requirements specified in ISO 23640 apply.

7 Training and education programs

7.1 Training of healthcare providers

The manufacturer shall design and validate a training program for healthcare providers. The training program shall educate healthcare providers in the proper use of the system, patient selection and patient education.

The training program for healthcare providers shall include recommended patient selection criteria and a description of user characteristics likely to predict success in using the system.

The predictive user characteristics should include:

— ability to understand the concept of oral-anticoagulant therapy and its risks;

— willingness to perform oral-anticoagulation self-testing and participate actively with a healthcare provider in documentation and information exchange for therapy adjustment;

— sufficient manual dexterity and visual acuity;

— demonstrated patient compliance.

In cases where the patient does not meet the criteria, the training program should advise that measurements may be carried out by trained relatives or other third parties who meet the selection criteria.

7.2 Education of lay persons

The manufacturer shall establish and provide an education program for lay persons. The program shall include the following elements:

— basic information about blood clotting and oral anticoagulation therapy;

— explanation of INR results;

— explanation of the patient-specific individual therapeutic interval;

— training in skin puncture and self-testing;

— tasks of users and healthcare providers in oral-anticoagulation self-testing;

— recordkeeping by the user and healthcare provider;

— description of control procedures and system self-checks;

— explanation of error codes and actions to be taken when they occur;

— emphasis on the proper interpretation of control results;

— actions necessary when control results are not within the target limits;

— protocol for communication between users and healthcare providers;

— actions necessary when results are not within the individual therapeutic interval;

— action necessary in the event of additional diseases, emergencies or accidents.

The education program shall provide sufficient technical knowledge regarding the general concept of oral anticoagulant therapy and shall teach practical skills to perform self-testing and control procedures.

An evaluation of the user's ability to perform self-testing properly shall be made on completion of the education program.

The evaluation should include a practical test of technical proficiency and/or a written test of comprehension.

NOTE Periodic re-evaluation of users to assess conformance and verify continuing competence can be advisable.

The manufacturer shall provide a method for documentation of successful completion of the education program by the user.

The training may be documented by the manufacturer or the healthcare professional.

7.3 Evaluation of user conformance in following the manufacturer's and the physician's instructions

The manufacturer shall recommend, in the instructions for use for the healthcare professional, suitable procedures for monitoring and evaluating user conformance with the manufacturer's and the physician's instructions, where applicable.

8 System performance validation

8.1 General

System performance validation studies shall be conducted as part of the manufacturer's design control system to demonstrate that the oral-anticoagulation monitoring system meets specifications for trueness, precision, and system accuracy.

The requirements specified in ISO 13485 apply.

NOTE Typically these studies do not include lay users of the device as this is captured in Clause 9.

8.2 Contributors to measurement uncertainty

Factors that affect the accuracy (precision and trueness) of INR results and contribute to measurement uncertainty shall be identified and taken into consideration when designing the validation protocol(s).

These factors include intra-individual biological variability, measurement uncertainty of the assigned value of the calibrator (lack of a higher-order reference material and limitations of the WHO reference measurement procedure), factor sensitivity differences, reagent lot-to-lot differences, reagent instability and measurement imprecision.

NOTE 1 Specificity with respect to interfering substances and effects of isolated coagulation factor deficiencies are not addressed in the system performance validation studies outlined in this document.

NOTE 2 The designated reference measurement procedure, the WHO tilt-tube method, is difficult to perform, highly dependent on user technique and valid only for INR values between 1,0 and 4,5. Attempts to develop a true calibrator have not been successful. The reference measurement procedure and calibrator can contribute significantly to increased measurement uncertainty of INR measurements.

Refer to Annex C for additional information/examples of calculations of measurement uncertainty.

8.3 System performance validation study

The system performance validation study shall be performed according to a written protocol. The protocol shall, as a minimum, specify the experimental details, data analysis procedures and acceptance criteria. Statistical designs, including the numbers of instruments, reagent units, sample replication and acceptance criteria, shall be justified in the protocol. The results of the performance validation study shall be documented in a report.

All components of the system selected for evaluation, including instruments, reagents and accessories, shall be representative of the product intended for sale.

The oral-anticoagulation monitoring system shall be adjusted prior to the validation study, according to the manufacturer's instructions (e.g. via coding, chips). No adjustments shall be made between replicate measurements unless the manufacturer's instructions specify an adjustment before each measurement.

The manufacturer's recommended control procedures shall be performed prior to each validation study.

The unique nature of INR measurements, the characteristics of the specific self-testing system and the instability of the specimens shall be considered when designing experimental protocols for verifying system performance.

The appropriate sample for each validation study is specified in 8.4 and 8.5. An alternative sample may be used to evaluate specific variables (e.g. instrument-to-instrument precision) if equivalence to fresh capillary blood is demonstrated.

NOTE Although individuals taking vitamin K antagonist are the intended users of the system, the protocol requires that specimens from a group of individuals not taking vitamin K antagonist be included in the study for the purpose of verifying acceptable accuracy (precision and trueness) throughout the measuring interval, including below the therapeutic interval.

Trained operators may perform the system performance validation studies. Lay persons perform the system performance studies described in Clause 9.

8.4 Validation of measurement precision

8.4.1 General

The measurement precision of the anticoagulation monitoring system used in self-testing shall be validated in actual or simulated conditions of use.

The repeatability and intermediate precision of measurement shall be validated against performance criteria derived from the system accuracy criteria in 8.6.1. The acceptance criteria shall be documented in the protocol.

Analysis of variance (ANOVA) is the preferred statistical method to use when multiple factors are evaluated. Choices of factors such as the number of instruments, reagent lots, and replicates for precision testing should be based on the sources of variability identified during risk assessment.

NOTE 1 Refer to ISO 5725-1 [3] for general principles regarding the evaluation of precision of a measurement method. The definitions and concepts of repeatability, reproducibility and intermediate levels of precision are described in ISO 5725-1 [3], ISO 5725-2 [5], ISO 5725-3 [6], and CLSI EP05 [21].

Because precision validation requires departure from the routine measurement procedure, such as taking multiple measurements from one or more samples, the data should be checked against objective validity criteria to detect effects of sample instability.

NOTE 2 Only limited validation of the reproducibility of INR measurements, reproducibility conditions can be made directly over time, across multiple lots, and across multiple analysts owing to the instability of blood specimens. The accuracy validation study (see 8.5) is designed to include the uncertainty due to these variables.

NOTE 3 Surrogate samples (e.g. control samples) and alternative evaluation approaches can be necessary to estimate the contribution of specific variables. Such evaluations are an essential part of design validation, but since study designs tend to be system-specific they are outside the scope of this document.

Differences in system performance can be observed depending on the state of illness of the persons on oral-anticoagulation therapy (e.g. chronically ill or acutely ill). The study population should reflect the intended use population, i.e. stabilized on anticoagulant therapy.

8.4.2 Validation of measurement repeatability

8.4.2.1 General

Measurement repeatability shall be evaluated from duplicate samples of capillary blood. To approximate repeatability conditions, both samples shall be taken, and measurements made within a short period of time.

The rationale for the experimental design shall be documented in the protocol.

NOTE Refer to ISO 5725-2 [5] for guidelines for determining the repeatability of a measurement procedure.

8.4.2.2 Samples

The repeatability validation study shall be performed with fresh capillary blood specimens from at least 45 persons receiving vitamin K antagonist therapy, and at least 15 persons not receiving therapy. These persons shall be selected so that INR values span the measuring interval of the system, with at least 15 persons in each of the intervals specified in Table 1.

Two samples shall be taken from each person by skin puncture (e.g. two separate fingersticks).

The INR value of each sample shall be determined using the oral-anticoagulation monitoring system.

The volume fraction of erythrocytes in blood (haematocrit) shall be within the interval claimed by the manufacturer.

Table 1 — INR intervals for validation of measurement repeatability

Interval	INR values
Nontherapeutic	< 2,0
Low therapeutic	2,0 to 3,0
High therapeutic	> 3,0 to 4,5
Supra-therapeutic	> 4,5

Appropriately validated surrogate sample materials may be used in place of actual persons' specimens for testing up to 20 % of the high therapeutic specimens, and 75 % of the supra-therapeutic interval.

NOTE If the manufacturer's measuring interval claim is up to 4,5 or lower, the supra-therapeutic interval does not need to be tested.

8.4.2.3 Instruments and reagents

Measurement repeatability may be validated using one or more instruments and one or more reagent lots. If more than one instrument or reagent lot is used, the experimental design shall allow analysis of repeatability within a single instrument and/or within a single lot.

8.4.3 Validation of intermediate precision

8.4.3.1 General

The validation of intermediate precision shall be conducted in normal conditions of use (i.e. by an individual user across multiple days with the same instrument).

Manufacturers shall utilize ANOVA to determine the significant sources of measurement uncertainty to include in the intermediate precision testing.

The intermediate precision conditions and rationale for the experimental design shall be documented in the protocol. As a minimum, manufacturers shall include the components of uncertainty due to lot-to-lot, instrument-to-instrument and day-to-day.

Intermediate t precision shall be validated across the entire measuring interval of the instrument.

NOTE Refer to ISO 5725-3 [6] for guidelines on determining intermediate measurement precision.

8.4.3.1.1 Samples

Intermediate precision shall be validated using liquid control materials or stable surrogate samples in the low therapeutic interval (INR 2,0 to 3,0), in the high therapeutic interval (INR 3,1 to 4,5), and at a high value close to the upper end of the measuring interval. Intermediate precision shall be validated across the entire measuring interval.

Samples shall be prepared according to the manufacturer's instructions for use. Stability of samples over the evaluation period shall be validated.

8.4.3.1.2 Instruments and reagents

At least three to five instruments shall be selected to validate the intermediate precision of the oral-anticoagulation monitoring system.

Multiple lots shall be used, and the experiment shall be designed to include lot-to-lot variability. The number of lots used shall be statistically justified (minimum = 3); if a partial lot(s) is used, then the rationale shall be recorded. The validation study can be performed on a single lot of reagent if data are available that demonstrate that intermediate precision is not significantly dependent on the reagent lot and the lot release criteria are such that between-lot imprecision is very small.

Reagent units shall be taken from at least ten vials or packages. The validation protocol shall ensure that data from the different variables (e.g. lot, instrument) are not confounded.

8.4.3.2 Validation procedure

The minimum design to verify intermediate precision over multiple days requires two measurements per day of each sample, per lot, for five days for each instrument. Taking two measurements per day allows the assessment of repeatability of the liquid control materials since these are a different matrix than the sample type used in the repeatability experiment in 8.4.2.

An example study design (using one sample) is shown in Figure 1.

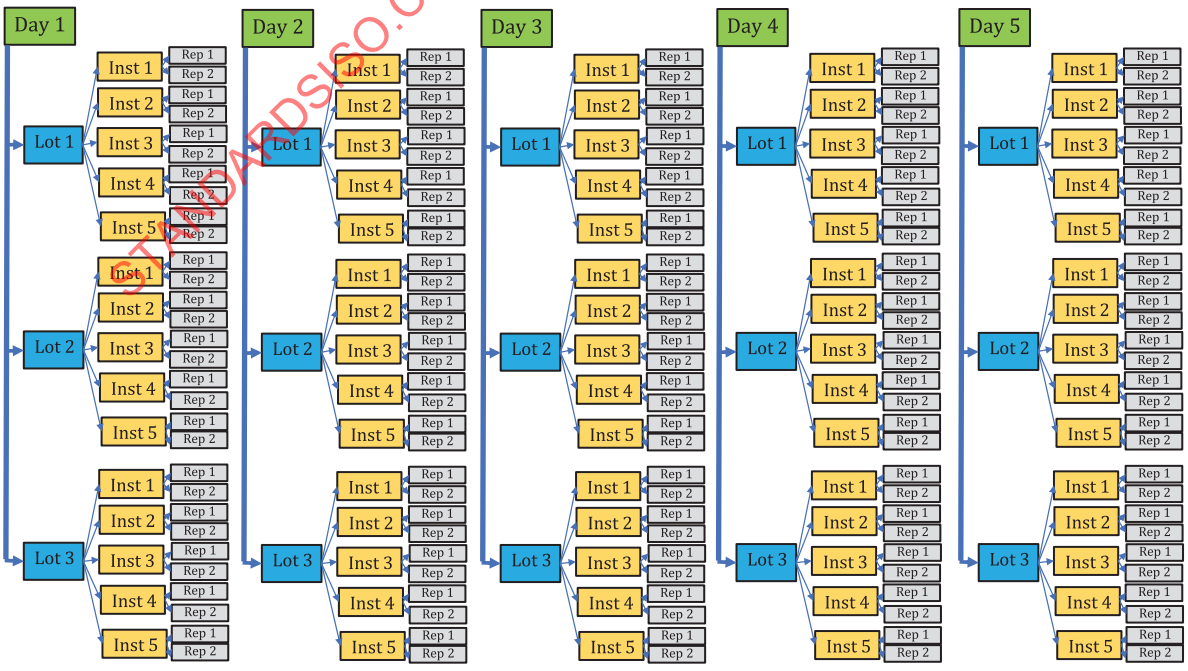


Figure 1 — Design for intermediate precision study

Alternatively, lot-to-lot imprecision may be assessed in a statistically equivalent study, e.g. with a minimum of three lots, one instrument, and one operator.

8.4.4 Data analysis

8.4.4.1 Data validity (identification of outliers)

Prior to analysis, data shall be evaluated to identify errors and evidence of sample instability. Obvious errors (e.g. transcription errors, insufficient sample volume) should be documented and corrected. No data may be eliminated without cause (i.e. for statistical reasons alone).

Sample instability, expressed as a drift in results, can be identified through statistical analysis of each sample's replicate results. The following guidelines apply.

a) For the repeatability data, calculate the duplicate range limit from all of the data. If precision is related to INR, then the duplicate range limit will also depend on INR as larger differences between replicates can be expected at higher INR values. The rationale for this limit is based on the statistical distribution of the range and also depends on the precision of the system. The limit is calculated by following these steps:

   1) Calculate the difference between the duplicate measurements for each sample.

   2) Calculate the average result for each sample.

   3) Obtain an estimate of within-sample precision from a statistically equivalent study or from the system specifications. As precision usually decreases with the INR, it should be expressed as a coefficient of variation (CV).

   4) For each patient specimen, multiply the average result by the CV and then by 4,2. This value is the duplicate range limit for that person.

   5) For example, suppose that two results for a person are 2,4 and 2,6. The average is 2,5. If a CV of 5 % is used as an estimate for within-person precision, then the duplicate range limit is 2,5 × 0,05 × 4,2, or 0,525. Since the actual difference is 0,2, it would be accepted. If the two replicates were 2,2 and 2,8, then the average would still be 2,5, but this difference would exceed the duplicate range limit. All data from the person is eliminated. Data from not more than two persons should be eliminated (< 3,5 %).

      NOTE 1 Duplicate differences exceeding the duplicate range limit have a 99,7 % probability that they are invalid data, which can be due to sample instability or drift [31].

   6) All results are part of the data set and should be reported. The estimate of precision should be performed with and without those results eliminated.

b) For intermediate precision, use all of the data to calculate the data exclusion limit. This limit is based on a run of 10 samples and is designed to detect either a high or low outlier. This value is calculated by following these steps:

   1) For each sample, calculate the average and standard deviation (SD) from the run of 10.

   2) Also determine the minimum and maximum value from the run of 10.

   3) Calculate the following statistics: (Maximum – Average)/SD and (Average – Minimum)/SD.

   4) Take the larger of the two numbers. This represents the possible suspect point.

   5) If the result of step b) 4 is larger than 2,48, then the suspect exceeds the data exclusion limit.

Data values exceeding the data exclusion limit have a 99 % probability that their extreme value is not due to the basic imprecision of the system. They should be considered as outliers. They represent cases of extreme performance that would not be expected in normal use [33].

NOTE 2 Guidelines for identifying outliers are found in ISO 5725-2:2019 [5] and in CLSI document EP05-A3 [21].

The following requirements apply to data exclusion:

c) For statistical outliers:

   1) Data determined to be statistical outliers shall not be discarded. Data analysis shall be performed, and results reported with and without the outliers included.

   2) For repeatability, exceeding the acceptable difference between duplicates indicates sample instability. Both measurements shall be considered invalid However, data analysis should be performed, and results reported with and without these samples.

   3) For intermediate precision, a trend exceeding the acceptable limit indicates sample instability. However, data analysis should be performed, and results reported with and without these samples.

d) For a procedural mistake or instrument malfunction occurred during testing:

   1) an investigation shall be conducted to determine the cause. The investigation and its conclusions shall be documented in the report.

   2) If a cause is found, the outcome from the affected sample shall be considered invalid and shall not be used in calculations.

   3) Data rejected for cause (e.g. confirmed analyst error) may be replaced with new measurement results.

   4) If a cause cannot be determined, data analysis shall be performed, and the results reported with and without the data in question.

8.4.4.2 Repeatability analysis

Estimation of repeatability with fresh capillary blood specimens in the precision study is performed for each of four INR intervals: Interval1 (nontherapeutic), Interval2 (low therapeutic), Interval3 (high therapeutic) and Interval4 (supra-therapeutic) separately. Subjects selected in the precision study shall be selected so that INR values span the measuring interval with at least 15 subjects in each of four intervals. Each subject has two measurements with two separate fingerstick $X_{i,1}$ and $X_{i,2}$; and an average ($Average_i$) and Standard Deviation (SD_i) using two measurements ($X_{i,1}$ and $X_{i,2}$) should be calculated for each person (i=1, 60). Present $Average_i$ and SD_i for all subjects in the study on plane (X,Y) where X-axis is the average value ($Average_i$) for a subject and Y-axis is the standard deviation (SD_i) for the subject. The data is analysed with regard to i determination of the number of subjects with $Average_i$ values from Interval1 (number of subjects is N1), Interval 2 (number of subjects is N2), Interval3 (number of subjects is N3) and Interval 4 (number of subjects is N4) [N1+N2+N3+N4=60].

Repeatability with fresh capillary blood specimens is estimated for each of four intervals separately in the following way:

Consider Interval 1 (N1 subjects have $Average_i$ INR results in Interval1). An example of the data where each interval has 15 subjects (N1=N2=N3=N4=15) is presented by Table 2.

Table 2 — Repeatability – Demonstration of samples in each interval

	Person ID	Replicate 1, $X_{i,1}$	Replicate 2, $X_{i,2}$	Average of 2 replicates	SD of 2 replicates	Var=SD*SD
Interval1 (nontherapeutic)	1					
	2					
	3					
	…					
	15					
Interval2 (low therapeutic)	16					
	17					
	…					
	30					
Interval3 (high therapeutic)	31					
	32					
	..					
	45					
Interval4 (supra-therapeutic)	46					
	47					
	..					
	60					

Repeatability analysis is performed and stated as follows:

a) The average variance of N1 variances for Interval 1 is the variance averaged over all subjects in Interval 1. For the example with N1=15, variance for Interval 1 is calculated as $Var_{Interval1}=(Var_1+Var_2+...+Var_{15})/15$.

b) Then calculate standard deviation of repeatability for Interval1 as $SD_{Interval1} = sqrt(Var_{Interval1})$.

c) The grand average of N1 average values from Interval1 is calculated. For the example with N1=15, the grand average is calculated as $Average_{Interval1}=(Average_1+Average_2+...+Average_{15})/15$.

d) CV for each of four intervals is calculated as $CV_{Interval1}=SD_{Interval1}/Average_{Interval1}$.

Results of repeatability analysis is presented as in Table 3.

Table 3 — Results of repeatability analysis

	N of subjects in Interval	Average in Interval	SD in Interval	%CV in Interval
Interval1	N1	$Average_{Interval1}$	$SD_{Interval1}$	$\%CV_{Interval1}$
Interval2	N2	$Average_{Interval2}$	$SD_{Interval2}$	$\%CV_{Interval2}$
Interval3	N3	$Average_{Interval3}$	$SD_{Interval3}$	$\%CV_{Interval3}$
Interval4	N4	$Average_{Interval4}$	$SD_{Interval4}$	$\%CV_{Interval4}$

In addition, the following information shall be reported for each subject:

a) Number of initial invalid results;

b) If invalid results were re-tested, number of re-tested invalid results and number of final invalid results.

In summary of excluded results:

— Number of invalid results excluded from statistical analysis;

— Whether other results were excluded including the method of identification and the results of the investigation.

8.4.4.3 Intermediate precision analysis

The average, standard deviation and CV for intermediate precision shall be calculated for each sample using documented statistical procedures.

ANOVA is the preferred method for data analysis for intermediate precision.

The following information shall be reported for each sample:

a) grand average of the observed INR values for each sample;

b) intermediate precision standard deviation with 95 % confidence interval and CV for INR values from each sample;

c) summary of any invalid data identified and excluded from statistical analysis, including the method of identification and the results of the investigation;

d) references to the statistical analysis procedures.

8.5 Validation of system accuracy

8.5.1 General requirements

System accuracy shall be validated in actual or simulated conditions of use.

The system accuracy validation study shall be designed to include systematic effects (bias) and random effects (imprecision) that would be experienced by an individual user in anticipated conditions of use.

NOTE 1 The relationship of accuracy to trueness and precision is discussed in ISO 5725-1.

The measurement procedure (comparator) used as a basis for system accuracy validation shall be preferably a reference measurement procedure, and at least of higher metrological order than that used for calibration of the lay-person's routine measurement procedure, and shall be linked to the WHO tilt-tube method through a separate unbroken pathway.

NOTE 2 If a reference measurement procedure is not available, it is preferred that the comparator measurement procedure be from a different manufacturer than that of the self-testing system using the same sample type.

The requirements specified in ISO 20916 apply.

8.5.2 Study population

Persons enrolled in the study shall meet the selection criteria as stated in 7.1 as part of the healthcare providers training with a description of user characteristics likely to predict success in using the system along with predictive user characteristics.

One hundred and eighty (180) vitamin K antagonist-treated persons shall be enrolled at a minimum of three sites. In addition, 20 persons not receiving vitamin K antagonist therapy shall be enrolled across the sites.

Demographic data, targeted INR and the indication for oral-anticoagulation therapy shall be recorded for each person on therapy, and demographic data for persons not on oral anticoagulation therapy. Demographic data shall include descriptions of the person's health conditions.

INR values of the study persons shall span the claimed measuring interval of the system, as measured by the manufacturer's standing measurement procedure or the alternative measurement procedure.

At least 5 % of the study persons (n = 10) shall have an INR value ≥ 4,6 (see Table 4 in 8.5.3). If the required number of patients with an INR above 4,5 cannot be obtained at the initial study sites, expansion of the study to additional sites can be necessary.

8.5.3 Samples/Specimen

Fresh capillary blood specimens shall be used for the validation of system accuracy. Alternatively, stabilized venous blood specimens may be used when equivalence of the venous specimens to fresh capillary blood specimens has been demonstrated.

For the comparator measurement procedure, the intended use sample shall be used.

Fresh capillary blood specimens shall be collected by skin puncture (e.g. fingerstick). Each specimen shall be collected with a separate finger puncture. Sample containers designed for the collection of capillary blood should be used, if applicable.

Samples shall be prepared from the specimens, which may be processed according to the instructions for use, including specimen pre-treatment if required.

Each sample shall have sufficient volume to be measured by the oral-anticoagulation monitoring system and at least in duplicate by the manufacturer's measurement procedure.

Exclusion criteria, such as the volume fraction of erythrocytes (packed cell volume, haematocrit), shall be based on the manufacturer's instructions for use and specified in the protocol. However, specimens spanning the claimed haematocrit interval shall be included.

The INR values shall be distributed only as specified in Table 4. Additional samples in a category will skew the results and are not allowed. INR values shall be determined by the manufacturer's measurement procedure.

Table 4 — INR values of samples for system accuracy validation

Number fraction of samples [a] %	INR values
10 to 15	< 2,0
15 to 40	2,0 to 2,8
15 to 40	>2,8 to 3,7
10 to 30	>3,7 to 4,5
5 to 10	> 4,5
[a] Once a category is filled (i.e. the maximum allowed percentage has been reached), no more samples may be added to that category.	

NOTE The number of samples was determined based on the evaluation of the tolerance interval against the performance criteria in 8.6.1 Table 5. Robustness of the Allowable Difference limits was evaluated by verifying the tolerance interval [27][29] (proportion=0,95, confidence=0,95) is contained within. Tolerance intervals for N=150, 200, 250 and with increasing values of the standard deviation (SD) were calculated. SD (difference) up to 0,15 for INR less than 2,0, SD (% difference) up to 9 for the INR interval of 2,0 to 4,5, and SD (% difference) up to 11 for INR greater than 4,5 were used. In all cases, the calculated tolerance intervals fell within the indicated limits.

8.5.4 Instruments and reagents

The system accuracy validation study data analysis may be performed with each person using one instrument.

If different persons use the same instrument, disinfection of the instrument is necessary to avoid potential transfer of bloodborne pathogens. Manufacturers should validate this procedure and include disinfection information in the instrument's user manual or instructions for use.

At least two reagent lots shall be included in the system accuracy validation study. The samples should be evenly distributed across the two lots, in a randomized manner.

8.5.5 Comparator measurement procedure

The manufacturer shall establish a comparator measurement procedure traceable to the manual tilt-tube reference measurement procedure using an IRP of thromboplastin.

The manufacturer should specify the type of thromboplastin (e.g. human recombinant, rabbit brain) used by the comparator method. Comparison to a method that uses the same type of thromboplastin as the monitoring system is preferred.

The procedure shall specify the collection procedure regarding the appropriate specimen (e.g. citrate concentration) and brand mark of the collection device.

The requirements specified in ISO 17511 apply.

The requirements specified in WHO Technical Report Series, No. 889, 1999, Clauses 5 and 6 apply.

A routine coagulation measurement procedure (e.g. in a hospital or outpatient clinic laboratory) that is traceable to the manual tilt-tube reference measurement procedure using an IRP of thromboplastin and is validated for precision and trueness by comparison to the manufacturer's selected or standing measurement procedure may be used to assign the reference values.

A detailed description of the measurement procedure used to determine the reference values, including traceability to the manual tilt-tube reference measurement procedure using an IRP of thromboplastin, or equivalence to the comparator measurement procedure, shall be documented in the protocol.

NOTE Examples of suitable traceability chains are shown in Figures B.1 and B.2.

If the manufacturer contracts with a reference measurement laboratory, then appropriate measures shall be taken to verify that the laboratory is qualified to perform the measurement procedure.

ISO 15195 [11] may be used as a guide.

8.5.6 Study design

System accuracy may be validated using either a one- or two-step comparison.

In the one-step comparison, capillary blood is compared to venous blood without anticoagulant (if claimed as an acceptable specimen type) and the appropriate reference method sample (e.g. citrated plasma).

In the two-step comparison, capillary blood is compared to venous blood without anticoagulant, and venous blood without anticoagulant is compared to the appropriate reference method sample (e.g. citrated plasma). This approach may be used if the relationship between venous and capillary blood is established.

Either procedure allows several replicates of each venous blood specimen to be measured. Therefore, an assessment of the different sources of variability (e.g. reagent lots, instruments, volume fraction of erythrocytes) may be made with increased statistical power.

Individual measurements from the oral-anticoagulation monitoring system shall be compared to reference INR values determined by a comparator measurement procedure (i.e. a selected or standing measurement procedure or another validated measurement procedure that has been shown to produce equivalent results).

8.5.7 Procedure

8.5.7.1 General

The manufacturer may choose to follow a one-step procedure or two-step procedure.

The following experimental designs represent the minimum requirements to verify system accuracy. The procedures may be modified to accommodate multiple reagent lots or other factors.

8.5.7.2 One-step procedure

Two capillary blood specimens shall be collected from each person, according to the manufacturer's instructions for use, for duplicate measurement on the oral-anticoagulation monitoring system.

Simultaneously, an appropriate reference specimen (e.g. citrated venous blood specimen) shall be collected from the person by an experienced phlebotomist in accordance with the requirements of the comparator measurement procedure (see 8.5.5). If the manufacturer intends the system to be used for venous, nonanticoagulated blood, this specimen type shall be collected. Venous blood without anticoagulant may be used for plasma testing, after addition of citrate anticoagulant and separation of platelet-poor plasma, if allowable for the measurement procedure.

The capillary specimens and venous blood specimens (if applicable) shall be measured on the system under evaluation, according to the manufacturer's instructions for use, and the result shall be recorded on the data collection sheet.

After measurement on the oral-anticoagulation monitoring system (if applicable), the venous blood specimen shall be processed and analysed by the manufacturer's standing measurement procedure or alternative measurement procedure (see 8.5.5) and the INR result shall be recorded on the data collection sheet.

The volume fraction of erythrocytes (haematocrit value) shall be measured on each specimen to verify that the value is within the acceptable interval specified for the system, if applicable. The results shall be recorded on the data collection sheet.

8.5.7.3 Two-step procedure

In the two-step procedure:

a) during the first step, the equivalency of venous and capillary blood shall be shown, and

b) during the second step, venous blood without anticoagulant as a specimen for the blood device, and the appropriate reference specimen (e.g. venous citrated plasma sample) for the respective comparison method from the same venous specimen, shall be used.

In the first step, two capillary blood specimens shall be collected from each subject according to the manufacturer's instructions for use, for duplicate measurement on the oral-anticoagulation monitoring system.

Simultaneously, a venous blood specimen shall be collected from the subject by an experienced phlebotomist, in accordance with the requirements of the self-testing system.

The specimens shall be measured on the system under evaluation, according to the manufacturer's instructions for use, and the result recorded on the data collection sheet.

Once capillary and venous blood without anticoagulant have been demonstrated to be equivalent, the second step comparison (i.e. between samples of venous blood without anticoagulant and the comparator specimen) can be undertaken. This comparison may be conducted at sites which are distant in time and place from the original capillary/venous equivalency studies.

NOTE 1 For the purposes of this document, "equivalent" means that systematic differences (biases) at the medical decision levels of 2,0, 3,5 and 4,5 INR are ≤5 % with appropriate 95 % confidence intervals.

In the second step, a venous blood specimen without anticoagulant shall be measured on the system under evaluation, according to the manufacturer's instructions for use, and the result recorded on the data collection sheet.

The venous blood specimen shall be processed immediately and measured by the reference measurement procedure (see 8.5.5) and the INR result shall be recorded on the data collection sheet.

The volume fraction of erythrocytes (haematocrit value) shall be measured on each sample to verify that the value is within the acceptable interval specified for the system. The results shall be recorded on the data collection sheet.

The two-step procedure is recommended for studies when finger sticks are not feasible (see Reference [42]).

NOTE 2 Finger sticks cannot be feasible because the inconvenience added for the patient due to two parallel punctures, one capillary and one venous, or can be:

— not accepted by the patients, they will not give informed consent, and/or;

— not accepted by the investigator, because difficulties in procedural timings are experienced.

8.5.8 Data analysis

8.5.8.1 General

Prior to analysis, the data sheets shall be evaluated to identify obvious errors (e.g. transcription errors, insufficient volume of blood sample). Corrections should be made as appropriate.

No data deemed valid by the study investigator may be excluded from the assessment of system accuracy. The following guidelines apply to the validation of system accuracy:

a) All procedural errors, instrument malfunctions and control failures shall be investigated to determine the cause. The investigation and its conclusions shall be documented in the report.

b) If a result was deemed valid by the study investigator, even though an error message was given, if a control limit was exceeded or if a procedural error occurred, such a result shall not be rejected. The reason that the user ignored the error message, control failure or procedural error shall be investigated.

c) The data shall be examined for statistical outliers by a procedure defined in the protocol. Regression and correlation analyses shall be performed and reported with and without the outlier data. Outlier data points shall be included in the plots using a different symbol. Guidelines for identifying outliers are found in ISO 5725-2:2019 [5] and in CLSI document EP09C [23].

Results shall be plotted and analysed, and the following information shall be reported:

— total number of samples/specimens analysed;

— interval of INR values, as measured by the comparator measurement procedure;

— graphical plots of the data with appropriate statistics (see examples in 8.5.8.2 and 8.5.8.3);

— results of the system accuracy assessment (see 8.6.2 and 8.6.3);

— summary of INR values that were excluded from statistical analysis due to exceeding instrument's measuring range;

— summary of outliers identified and excluded from statistical analysis, including the procedure for identifying the outliers and the outcome of the investigation into their cause;

— literature references for the statistical analysis procedures.

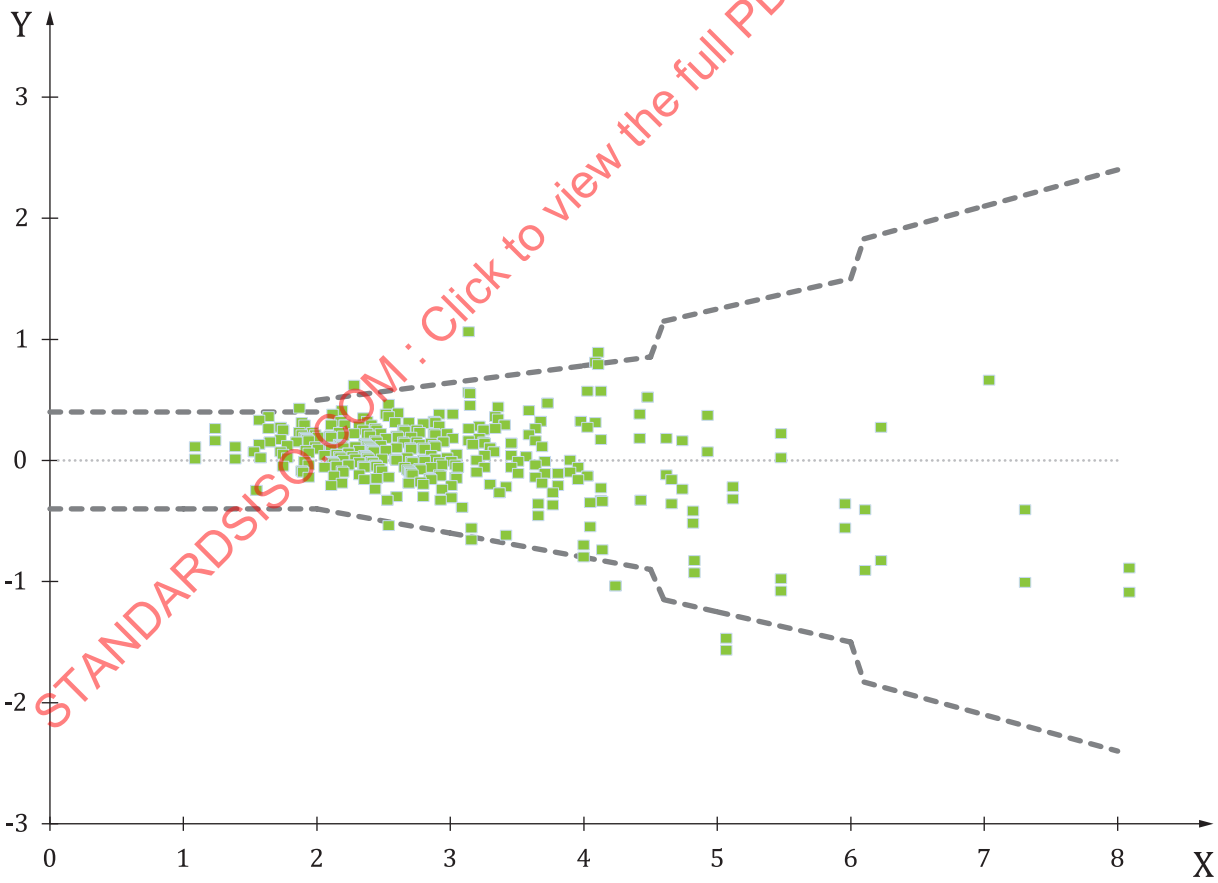
8.5.8.2 Difference plots

The difference between individual results from the oral-anticoagulation monitoring system and the reference values shall be plotted as the dependent variable. The reference values shall be plotted as the independent variable. Reference values may be averages of replicate measurements.

Difference plots are useful for visually demonstrating the magnitude of the bias over the entire range of INR results.

Plotting percentage difference against INR values at low INR values is generally not suitable for the graphical evaluation of system accuracy. Actual INR differences should be used. A recommended cut-off value is 2,0 INR.

EXAMPLE A plot of results from a validation study of an oral-anticoagulation monitoring system is illustrated in Figure 2. The upper and lower lines represent the acceptance criteria from 8.6.1.



Key

X comparator measurement procedure value (INR)

Y anticoagulation monitoring device value (INR) comparator value

Dotted line (- - - -) Allowable difference

Figure 2 — INR difference plot

Assessment of system accuracy shall be based on all data deemed valid by the study investigator. The following statistics shall be reported for each INR range in Table 3:

a) Bias between the oral-anticoagulation monitoring system results and the reference values.

b) Percent of results within the acceptability criteria for system accuracy described in 8.6.1. Also, see 8.6.2.

c) INR interval that encompasses 95 % of the differences.

8.5.8.3 Regression analysis

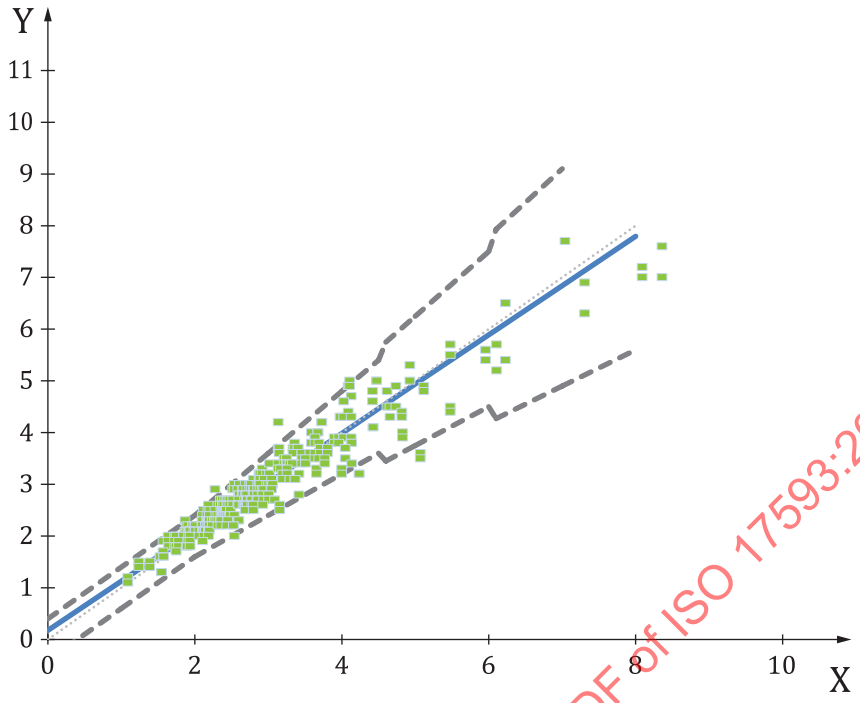
Individual results of the oral-anticoagulation monitoring system shall be plotted as the dependent variable and the comparator values as the independent variable. Comparator values may be averages of replicate measurements. Identical scales and intervals shall be used for the x- and y-axes.

The slope and y-intercept shall be calculated by a suitable regression analysis procedure. The method used shall be specified in the protocol.

NOTE 1 Examples include linear regression, Deming regression, orthogonal regression (a special case of the Deming regression) or Passing-Bablok regression. Appropriate regression analysis depends on the data meeting certain statistical assumptions. For an evaluation of regression procedures for method comparison studies and guidance in selecting an appropriate regression analysis procedure, see Linnet [30] or Stöckl [37].

NOTE 2 Bias can be calculated from the regression equation at selected INR values (e.g. at decision points such as 2,0, 3,5, 4,5). See CLSI document EP09C [23].

EXAMPLE A scatter plot from a validation study of an oral-anticoagulation monitoring system is illustrated in Figure 3. The two outer lines represent the acceptance criteria from 8.6.1. The regression slope is 0,952 4 (confidence interval 0,909 1 to 1,000 0); the y intercept is 0,176 2 (confidence interval 0,072 64 to 0,263 6); the correlation coefficient is 0,960.



Key

X comparator measurement procedure value (INR)

Y anticoagulation monitoring device value (INR)

Black dotted line Dotted line (- - - -) allowable difference

Solid blue line (——) Passing-Bablok fit (Y = 0,176 2 + 0,952 4X)

Figure 3 — Scatter plot with regression analysis

The following items shall be reported for each evaluation site:

— a scatter plot with regression analysis line and the y = x line;

— the slope and intercept of the linear regression line with confidence intervals;

— the Pearson's correlation coefficient *r*.

Outlier data can have an undue influence on estimates of central tendency and dispersion. Statistical parameters should be calculated with and without outlier data, and all data shall be shown in the regression plot, with outlier data points indicated by a different symbol.

8.6 Minimum acceptable system accuracy

8.6.1 System accuracy requirement

The minimum acceptable accuracy for results produced by an oral-anticoagulation monitoring system for self-testing shall be as follows:

— Overall agreement of ninety-five percent (95 %) of the differences between results from the oral anticoagulation monitoring system and results from the reference measurement procedure, in the combined INR ranges shall be within the limits in Table 5.

Table 5 — Performance criteria

INR interval	Allowable difference
< 2,0	±0,4
2,0 to 4,5	±20 %
>4,5 to 6,0	±25 %
> 6,0	±30 %

NOTE 1 The allowable differences are based on the performance of currently marketed anticoagulation monitoring systems, which represent the state-of-the-art. These systems have been shown to offer significant benefits to patients. See [28], [31].

NOTE 2 The criteria apply to system accuracy validation studies in which professional system operators have received proper training, the system has been properly maintained, and required adjustment and control procedures have been followed, in accordance with the manufacturer's instructions for use.

8.6.2 System accuracy assessment

Acceptability of the oral-anticoagulation monitoring system shall be determined using all of the 400 results obtained from the 200 persons. The total number of acceptable results in each INR interval shall be added to determine the number of acceptable results. The percentage of acceptable results is calculated as the number of acceptable results times 100, divided by the total number of results.

8.6.3 Data presentation

Results in the INR intervals in Table 5 shall be presented separately because of the allowable differences for each interval; see 8.6.1.

The results shall be presented in a table for each INR interval.

Recommended formats for healthcare professionals and lay persons are shown in Tables 6, 7 and 8. The data are from the example in 8.5.8.2. The interval represents the INR values evaluated in 8.6. The upper limit of the measuring interval may be higher; see 4.2.

Table 6 — Example of presentation of system accuracy results for professional labelling for INR below 2,0

INR interval	Within 0,3 INR	Within[a] 0,4 INR	Within 0,5 INR	Average INR difference
Below 2,0	94 %	98 %	100 %	0,11

[a] The shaded cells in the table represent the allowable difference for each INR interval per Table 5.

Table 7 — Example of presentation of system accuracy results for professional labelling for INR 2,0 and above

INR interval	Within 10 %	Within[a] 20 %	Within 25 %	Within 30 %	Average INR difference
2,0 to 3,5	81 %	98 %	99 %	100 %	0,06
INR interval	**Within 10 %**	**Within 20 %**	**Within 25 %**	**Within 30 %**	**Average INR difference**
3,6 to 4,5	70 %	95 %	100 %	100 %	0,34
INR interval	**Within 10 %**	**Within 20 %**	**Within 25 %**	**Within 30 %**	**Average INR difference**
4,6 to 6,0	68 %	86 %	91 %	95 %	0,51

[a] The shaded cells in the table represent the allowable difference for each INR interval per Table 5.

Table 7 *(continued)*

INR interval	Within 10 %	Within 20 %	Within 25 %	Within 30 %	Average INR difference
>6,0	45 %	100 %	100 %	100 %	0,78
[a] The shaded cells in the table represent the allowable difference for each INR interval per Table 5.					

Table 8 — Example of presentation of system accuracy results for lay person labelling

INR interval[a]	% acceptable results
1,1 to 7,7	97 %
[a] System accuracy was evaluated over this interval of INR results.	

9 Lay person performance evaluation

9.1 General

A lay person performance evaluation shall be performed by the manufacturer prior to placing a new oral-anticoagulation monitoring system into commercial distribution. The requirements specified in ISO 20916 apply.

The purpose of the lay person performance evaluation is to demonstrate that users can operate the oral-anticoagulation monitoring system and obtain acceptable results, given only the instructions for use and training routinely provided by the manufacturer.

The lay person performance evaluation shall be performed according to a written protocol. The protocol shall, as a minimum, specify the training and education, evaluation sites, data collection and analysis procedures and acceptance criteria. The results of the user performance evaluation shall be documented in a report.

Results obtained by the lay persons either may be compared to results obtained by experienced technicians, using the same oral-anticoagulation monitoring system, or may be compared to results obtained by the manufacturer's selected/standing measurement procedure, or both

9.2 Study overview

The lay person performance evaluation occurs as shown in Figure 4.

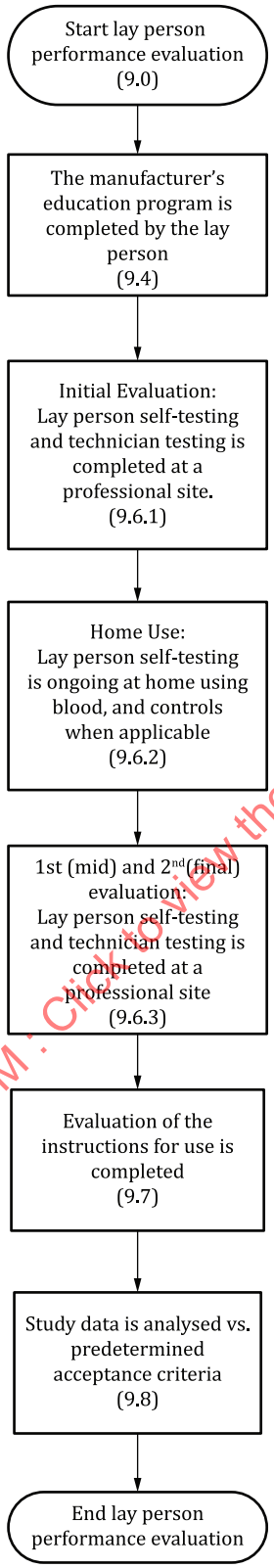


Figure 4 — Lay person performance evaluation study design

9.3 Study sites

Lay person studies shall be conducted at three professional sites. The setting shall allow the lay person to perform the measurements using only the instructions for use and training routinely provided to lay persons by the manufacturer. Rationale for the selection of the evaluation sites shall be documented.

NOTE The manufacturer is encouraged to select sites that represent the actual use of the product (e.g. anticoagulation clinics).

9.4 Subjects

At least 80 lay persons (subjects), roughly 26 per site, shall be included in the study. The age, gender and education level of these subjects needs to be representative of the intended user population. Subjects shall have a target INR interval between 2,0 and 4,5 and shall meet the requirements of the oral-anticoagulation self-testing system (e.g. the value for the volume fraction of erythrocytes shall fall within the interval specified in the instructions for use). Subjects to be included in this study should be stable on their warfarin treatment.

Consider recruiting more than 27 lay persons at each site to ensure the minimum data results needed for analysis are met in 9.8.

Subjects shall complete the manufacturer's education program, but shall not receive additional training, instructions, assistance or training materials other than those routinely provided with the oral-anticoagulation self-testing system.

Once the subjects have completed the manufacturer's education program and are deemed qualified to perform self-measuring, they can start the lay person study.

If the training program requires subjects to take the self-testing systems home, the subjects shall be instructed not to use the results for any medical purpose. The systems shall be labelled appropriately (e.g. "For Performance Evaluation Only", "For Investigational Use Only").

9.5 Instruments and materials

Lay person studies shall be conducted using one instrument and one reagent lot.

9.6 Evaluation of lay person proficiency

9.6.1 Initial evaluation

At the evaluation site, the subjects shall perform their own finger punctures and measure their blood value using the oral-anticoagulation self-testing system, as per the instructions for use. Each subject shall perform the measurement twice, obtaining two INR results. The site's trained healthcare provider shall also measure the subject's blood value using the same oral-anticoagulation self-testing system and the same lot of reagent. The healthcare professional shall measure the subject's blood twice, obtaining two INR results.

If two instruments are available, and if allowable by the self-testing system's instructions for use, the two measurements may be taken from a single finger puncture, using two sequential drops of blood and no excessive squeezing. The second drop(sample) shall be collected immediately as to avoid clotting.

Immediately thereafter, the healthcare provider may obtain a venous blood specimen from the subject for measurement by the manufacturer's selected/standing measurement procedure.

In order not to introduce bias, the order of measurement by the lay persons and the healthcare providers should be randomized or alternated.

Lay person techniques in operating and maintaining the system, applying the sample and reading the result shall be evaluated by the site's trained healthcare provider. Results of the evaluation shall be documented.

Lay persons may be given a questionnaire to evaluate their understanding of the system.

NOTE The training centre determines the pass/fail criteria for the questionnaire, depending on national regulations.

9.6.2 Home use

After completion of the initial evaluation, each lay person shall be provided with an oral anticoagulant monitoring system and instructed to perform measurements at home.

Each lay person shall be instructed to complete at least six measurements, one measurement per week for six weeks, following the manufacturer's instructions for use, including the measurement of control materials as applicable.

Each lay person shall be instructed to measure two control samples with each measurement, obtaining a total of six values for each level of control material, if applicable.

Manufacturers shall provide the lay persons with data forms for documentation of their self-testing results and control results.

9.6.3 Mid and final evaluation

Each lay person shall return to the healthcare provider's site twice during the six-week period, with the second/final visit being six weeks. The first/mid visit can be scheduled at any time but shall not be the same day as the second/final visit and ideally at three to four weeks. At each visit the lay person shall perform the proficiency evaluation. At the healthcare provider's site, the lay persons shall perform their own finger punctures and measure their blood specimens using the oral-anticoagulation self-testing system.

Immediately after the lay-person's self-testing, the site's trained healthcare provider shall measure the lay person's blood with the same oral-anticoagulation self-testing system.

Immediately thereafter, the healthcare provider shall obtain a venous blood specimen from the subject, for measurement by the manufacturer's selected/standing measurement procedure.

User techniques in operating and maintaining the system, applying the sample, and reading the result shall be evaluated by the trained healthcare provider participating in the study. Results of the user evaluation shall be documented in the report.

Subjects may be given a questionnaire designed to evaluate their understanding of the system. The questionnaire only needs to be given at the final visit.

Linear regression may be used to calculate the relationships of the patient and professional results against each other and against the manufacturer's selected/standing measurement procedure, respectively.

9.7 Evaluation of instructions for use

Instructions for use shall be evaluated by the study participants at the final visit. The lay persons and healthcare providers shall be requested to review and provide comments regarding the ease of understanding of the instructions for use.

This evaluation may be combined with the study described in 9.6 or may be conducted separately.

User comments may be collected via questionnaires, or as part of human factors studies.

The manufacturer shall establish acceptance criteria for the results of the evaluation of the instructions for use. If the users' results fail to meet the acceptance criteria, then the manufacturer shall consider the need to revise sections of the instructions and repeat the evaluation.

9.8 Acceptance criteria and data assessment

From either the user's duplicate results, and the healthcare provider's duplicate results or the results from the manufacturer's selected/standing measurement procedure, or both, repeatability of the duplicate measurements shall be calculated as described in 8.4.4.2. The repeatability % CV point estimate of both the user's and the healthcare provider's duplicate results should be ≤ 6 and ≤ 5 % respectively.

From the user's control results, if applicable, the intermediate precision SD shall be calculated using an analysis-of-variance procedure for each level of control material.

The first result from each set of duplicate results from both the mid and final visit (n= approximately 160) will be used for the analysis. Agreement of the user's results with the manufacturer's selected/ selected measurement procedure results shall be calculated as described in 8.5.8.

NOTE The healthcare provider's accuracy requirement to the manufacturer's selected/standing measurement procedure was assessed in Clause 8 and is not required to be performed again.

For the users' and the results of the manufacturer's selected/standing measurement procedure, 95 % of all results in the INR interval of 2,0 to 4,5 shall be within +/− 20 %.

The results of the study shall be reported in the format described in 8.6.3.

Annex A
(normative)

Additional requirements for electromagnetic compatibility

A.1 General

This annex specifies minimum requirements for immunity and emissions regarding electromagnetic compatibility (EMC) for oral-anticoagulation monitoring systems intended for self-testing, in addition to the requirements of 6.4.

If risk analysis (see 4.4) shows that exposure to higher levels of radiation or electrostatic discharge presents an unacceptable risk to the user, then the system shall be tested at these higher levels.

A.2 Immunity test requirements

A.2.1 Radiated immunity

The requirements specified in IEC 61000-4-3 apply.

In addition, immunity against radiated frequencies shall be extended to the frequency range up to 2,5 GHz, at a test level of 3 V/m.

A.2.2 Electrostatic discharge immunity

The requirements specified in IEC 61000-4-2 apply.

For air discharge, electrostatic discharge immunity shall be demonstrated at test levels of ±2 kV, ±4 kV and ±8 kV.

For contact discharge, electrostatic discharge immunity shall be demonstrated at test levels of ±2 kV, ±4 kV and ±6 kV.

A.3 System test requirements

If other equipment is connected to the instrument or can be connected to the instrument, the resulting system shall also fulfil the EMC requirements.

When determining system testing requirements, the manufacturer shall consider whether or not it is possible to perform a measurement while the system is connected. System configurations specified by the manufacturer, or foreseeable system configurations identified by risk analysis, shall be tested as described in A.2 if they allow the user to perform an INR measurement.

System test requirements may not apply if the design of the system prevents the user from performing INR measurements when the instrument is connected to other equipment.

A.4 Instructions for use

The instructions for use (see 5.3) shall include the following information:

a) a statement that the equipment complies with applicable EMC emission requirements, and that emissions of the energy used are low and not likely to cause interference in nearby electronic equipment;

b) a statement that the equipment is tested for immunity to electrostatic discharge, as specified in IEC 61000 4-2;

c) recommended mitigation measures that should be taken by the user to avoid incorrect operation or damage to the system;

EXAMPLE 1 "Do not use this instrument in a dry environment, especially if synthetic materials are present. Synthetic clothes, carpets, etc. can cause damaging static discharges in a dry environment."

d) a statement that the equipment is tested for immunity to radio frequency interference at the frequency range and test levels specified in this document;

e) recommended mitigation measures that should be taken by the user to avoid radio frequency interference, with specific examples.

EXAMPLE 2 "Do not use this instrument near cellular or cordless telephones, walkie talkies, garage-door openers, radio transmitters, or other electrical or electronic equipment that are sources of electromagnetic radiation, as these can interfere with the proper operation of the instrument."

Annex B
(informative)

Traceability chain examples

The diagram in Figure B.1 is adapted from ISO 17511 to show a full traceability chain for calibration of an oral anticoagulation monitoring system by the manufacturer.